UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/457,931	12/08/99	SNODGRASS H	441472000100

HM12/0718

MORRISON & FOERSTER LLP
755 PAGE MILL ROAD
PALO ALTO CA 94304-1018

EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	15

DATE MAILED: 07/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Acti n Summary	Application No. 09/457,931	Applicant(s) SNODGRASS, H. RALPH	
	Examiner Janet Kerr	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *19,20 and 34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Group I, in Paper No. 13 is acknowledged.

Claims 1-41 are pending.

Claims 19, 20, and 34-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Claims 1-18 and 21-33 are being examined on the merits.

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 21-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolating embryonic stem cells to generate embryoid bodies from species in which embryonic stem cells have been known to be isolated, does not reasonably provide enablement for generating embryoid bodies from embryonic stem cells from species in which such cells have not been previously isolated. In addition, the specification is not enabling

for all of the claim-designated methods of detecting changes in protein and gene expression in embryoid bodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to using embryoid bodies in a method of creating molecular profiles of chemical compositions, compiling libraries of molecular profiles, and methods of toxicity typing and ranking toxicity of a test chemical composition.

While the specification discloses the development of embryoid bodies from a specific mouse embryonic stem cell line, the specification does not disclose other methods for obtaining embryoid bodies or embryoid bodies from other species. While methods of embryonic stem cells has been established for a limited number of mammalian species, embryonic stem cell technology has not advanced such that isolation of embryonic stem cells from any mammalian species is routine and predictable. For example, Seamark (Reproductive Fertility and Development, 6:653-657, 1994) indicates that totipotency for ES cell technology in many livestock species has not been demonstrated (see, e.g., Abstract). Similarly, Matsui *et al.* (Cell, 1992) teach that while it is well established that pluripotential stem cells can be derived from the epiblast of blastocysts in culture, it is crucial to determine whether blastocyst-derived stem cells differ in their full range of developmental potencies and properties (see, e.g., page 845, right column, 2nd paragraph and page 846, left column, 2nd full paragraph). As embryonic stem cells are required in the generation of the embryoid bodies of the instant invention, and are essential to the claimed invention, the use of mammalian embryoid bodies are limited to those established in the art, thus, for example, methods directed to human embryoid bodies are non-enabled as the specification and the prior art does not provide guidance as to how to obtain embryonic stem cells from humans.

With regard to the claim designated methods, as claimed, the methods read on in situ analysis of alterations in protein or gene expression in the embryoid bodies. As such, the methods are non-enabling as the specification does not provide any guidance as to how to record alterations in gene expression or protein expression in the mammalian embryoid body. It is also

noted that claims do not recite that the changes in protein or gene expression are compared to protein or gene expression patterns observed in embryoid bodies not subjected to a chemical composition. It is unclear how one of skill in the art would know that changes in gene or protein expression have occurred. The specification generally teaches that methods of monitoring gene expression and protein expression are known in the art, however, there is no guidance in the specification as to how to utilize these methods of monitoring for the purpose of creating a molecular profile, or compiling a library of molecular profiles or for typing toxicity of a test chemical composition. Thus, the specification does not provide sufficient guidance to detect alterations in gene expression by a nucleotide hybridization assay, or alterations in protein expression by an "immunoactivity assay", for example, such that the detecting methods are consistent and reproducible. With regard to mass spectrometry assays, the specification discloses changes in protein spectra obtained by mass spectrometry. However, there is no correlation in the specification between changes in protein expression and toxicity *per se*. The state of the art also suggests that while methods of determining alterations in gene expression may be useful, significant hurdles remain with this technology. For example, Flint (Toxicology in Vitro, 12:591-595, 1998) teaches that with regard to gene chip technology for identifying compound-specific patterns of gene induction, a significant problem is that using this technology has yet to be validated. It is not known whether characteristic patterns of gene induction will be observed nor whether these will be classified according to broad classes of toxic effect or may differ between each chemical tested (see, e.g., page 592, left column).

Based on the limited guidance in the specification, and the state of the art with respect to obtaining embryonic stem cells from all mammalian species and with respect to the validity of methods directed to determining the toxicity of chemicals in vitro, it would require undue experimentation to practice the methods commensurate in scope with the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 and 21-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 21-23 are rendered vague and indefinite by the phrase "a molecular profile of a chemical composition" because it is unclear what is meant by "molecular profile"; it is also unclear how the alterations in gene expression or protein expression in the mammalian embryoid body are recorded. Is the recording done *in situ*, are the proteins or genes initially extracted from the embryoid body and further analyzed for alterations in protein or gene expression? How is it determined that protein or gene expression is altered, i.e., are the genes/proteins expressed in the embryoid body contacted with the chemical composition compared to embryoid bodies not subjected to the chemical composition? The metes and bounds of the claim are unclear.

Claim 8 is rendered vague and indefinite by the phrase "immunoactivity assay" as it is unclear what type of assay this encompasses, i.e., an assay of the activity of a population of immune cells?

Claims 21 and 22 are further rendered vague and indefinite by the phrase "type of toxicity" as it is unclear what is meant by this phrase, i.e., is toxicity type related to the relative toxicity of the chemical composition, the cell lineage affected by the chemical composition? The metes and bounds of the claim are unclear.

Claim 23 is rendered vague and indefinite by the phrase "ranking toxicity" because it is unclear if the composition is ranked relative to its toxicity or relative to the cells that are affected by the composition. The metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Ling *et al.* (J. Cell. Phys., 171:104-115, 1997).

The claims are directed to a method of creating a molecular profile of a chemical composition comprising the steps of contacting an isolated mammalian embryoid body with a chemical composition and recording alterations in protein expression in the embryoid body in response to the chemical composition to create a molecular profile of the chemical composition (claim 1), wherein the alterations in protein expression are detected by a label (claim 3) and wherein the label is fluorescent (claim 4).

Ling *et al.* teach a method comprising contacting an isolated mammalian embryoid body with a chemical composition comprising LIF, IL-11 or IL-6, and recording alterations in protein expression (i.e. cell surface marker expression) using a fluorescent label (see, e.g., page 105, under "Cells" and "Immunophenotyping", page 107, right column, continuing on page 109, left column, and Figure 7).

As Ling *et al.* teach all of the method steps of the claim, Ling *et al.* anticipates the claimed invention.

Claims 1, 2-4, 7, 14-18, 21-24, 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Spielmann *et al.* (In Vitro Toxicity, 10:119-127, 1997, spring issue).

Spielmann et al teach a method of using mouse embryonic stem cells *in vitro* for embryotoxicity testing comprising culturing the embryonic stem cells to a stage where the cells form embryoid bodies, contacting the bodies with a variety of chemical compositions, and determining the cytotoxicity of the chemical compositions by changes in protein expression, i.e., via the MTT cytotoxicity assay. Spielmann *et al.* also teach compiling libraries of the "molecular profiles", and ranking the chemical compositions with respect to their relative toxicities. See, e.g., page 120, Figure 1, see "materials and methods", "Results and Discussion" on pages 122-126, and Table 1).

Thus, the teachings of Spielmann *et al.* anticipate the claimed invention.

Claims 1, 3-5, and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Wobus *et al.* (U.S. Patent No. 6,007,993, 1999, effective filing date of 2/24/98).

Wobus *et al.* teach an in vitro test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem cells or embryonic germ cells obtained from primordial germ cells of the mouse or rat. A differentiation-dependent expression of tissue-specific genes of embryonic stem cell clones or embryonic germ cell clones is furnished in the presence of teratogenic substances. The substances act at specific times of the *in vitro* differentiation and subsequent differentiation. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected (see, e.g., column 2, lines 53-67). The cell clones contain reporter gene constructs which can be specifically activated, repressed or modulated in the course of the differentiation by exogenic test substances, such as retinoic acid, and the differentiation-dependent expression during the test procedure can be carried out by embryoid body differentiation in different lines (see, e.g., column 3, lines 1-23). The reporter gene can be LacZ or the luciferase

gene and detection can be by a simple staining reaction (see, e.g., column 3, lines 53-63). Promoters of the reporter gene constructs can be neuronal, cardiogenic, muscle and skeletal specific to monitor development (see, e.g., column 4, lines 2-14) in the presence of the exogenic test substance.

As Wobus *et al.* teach recording alterations in gene expression by monitoring protein expression after contacting an embryoid body with a chemical composition, and wherein the change in expression is detected by a colorimetric label, the reference of Wobus *et al.* anticipates the claimed invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600